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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/484,542	06/07/95	BRADER	M X-10097

EXAMINER	
ART UNIT	PAPER NUMBER
18M1/0625	1817 9

BANNER & ALLEGRETTI LTD
ELEVENTH FLOOR
1001 G STREET NW
WASHINGTON DC 20001-4597

DATE MAILED: 06/25/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

- ☒ This application has been examined ☒ Responsive to communication filed on 3/25/97 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12, 25 & 26 are pending in the application.
Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-12, 25 & 26 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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Part III DETAILED ACTION

Status of Claims

1. Claims 1-12, 25 and 26 are pending in this Office action. Claims 13-24 have been canceled.

Response to Amendment

2. The rejection of claims 1-26 under 35 U.S.C. § 112, second paragraph is withdrawn in light of applicant's arguments and amendments to the claims.

3. The rejection of claims 1-3, 13 and 14 are rejected under 35 U.S.C. § 102(a) as being anticipated by Havelund et al. [WO 95/07931] is moot with respect to claims 13 and 14 due to cancellation of the claims. The rejection is maintained with respect to claims 1-3 because the declaration of Michael J. Beckage filed 3/17/97 is defective. Although this declaration provides evidence convincing to one of ordinary skill in the art of reduction to practice of production of Lys^{B29}-palmitoyl human insulin prior to 3/23/95, the date of the Havelund et al. reference, the declaration has not been signed by all inventors as required under 37 C.F.R. 1.131(a). Submission of a declaration signed by all inventors would overcome the instant rejection.

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4. The rejection of claims 1-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Havelund et al. [WO 95/07931] in view of Hashimoto [*Pharm. Res.* **6**, 171-176 (1989)] and Howey et al. [*Diabetes* **43**, 396-402 (1994)] is moot with respect to canceled claims 13-24, and is maintained with respect to claims 1-12, 25 and 26.

The Havelund et al. reference is considered valid prior art for the reasons discussed in paragraph 3 above. Applicants response is silent with respect to Hashimoto and Howey et al., and therefore the instant rejection is maintained essentially for the reasons discussed in the previous Office action (paper 4). Submission of the declaration signed by all inventors would overcome the instant rejection.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1-12, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muranishi et al. [Japanese Application No. 1-254,699; art of record] in view of Hashimoto [*Pharm. Res.* **6**, 171-176 (1989); art of record] and Howey et al. [*Diabetes* **43**, 396-402 (1994); art of record].

Muranishi et al. teaches fatty acid acylated insulin derivatives, including N-palmitoyl Lys^{B29} insulins. Muranishi et al. fail to teach N^ε-(acylated/palmitoyl)-Lys^{B28}Pro^{B29}-human insulin, Zn-containing insulins, or formulations thereof having a specified pH range. Hashimoto et al.

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teach the synthesis and administration of palmitoylated insulins, including insulins in which the Lys^{B29} residue is palmitoylated, while Howey et al. teaches Lys^{B28}Pro^{B29}-human insulin and its Zn-complexed forms for treatment of diabetes mellitus. It would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the Zn-containing palmitoyl forms of insulin disclosed by applicants by either adding Zn to the Lys^{B29}-palmitoyl insulin of Muranishi et al., or to palmitoylate the Lys^{B28} position of the Lys^{B28}Pro^{B29}-human insulin of Howey et al. Motivation to add Zn to an insulin analog is provided by both the teachings of Howey with respect to the Zn binding properties of the Lys^{B28}Pro^{B29} derivative (see page 397 col. 1) and by the art-recognized fact that Zn is a normal constituent of native insulin which is an important determinant of its conformational properties. Motivation to produce palmitoyl Lys^{B28}Pro^{B29}-human insulin is provided by the expectation that the time profile of absorption of this derivative would be altered to produce a derivative whose activity profile might be both fast acting and of prolonged duration.

7. No claims are allowed.

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General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benet Prickril whose telephone number is (703) 305-5933. The examiner normally can be reached Monday through Thursday between 7:30 AM and 5:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703)308-3890. The fax phone number for Art Unit 1813 is (703) 305-7939.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.